Journal of Surgical Oncology 62:75–77 (1996)

GUEST EDITORIAL

Sentinel Lymphadenectomy in Primary Breast Carcinoma: An Alternative to Routine Axillary Dissection

ARMANDO E. GIULIANO, MD
From the Joyce Eisenberg Keefer Breast Center, John Wayne Cancer Institute at Saint John's Hospital and Health Center, Santa Monica, California

Despite the fact that axillary node status is the single most important prognostic indicator for patients with primary breast carcinoma, techniques for detecting axillary involvement have not changed much during the last quarter of a century. Axillary lymphadenectomy (ALND) with examination of the surgical specimen remains the gold standard. Physical examination has proved unacceptable for determining axillary status: up to 35% of axillary lymph nodes that are normal on physical examination contain carcinoma, whereas 25% of enlarged lymph nodes do not contain malignant cells. Imaging techniques also have not been satisfactory: mammography, computed tomography (CT), and magnetic resonance imaging (MRI) cannot distinguish benign from malignant nodes, and positron emission tomography (PET) seems to be useful only when abnormal nodes are larger than 1 cm [1]. A "metastatic index" is an appealing concept, but no combination of clinical and biological variables has reached an acceptable degree of accuracy [2].

ALND remains the only reliable method for determining lymph node status. But how much ALND is required for accurate staging? Complete ALND removes levels I, II, and III axillary nodes. Partial ALND removes levels I and II (or any ill-defined portion thereof), and axillary sampling removes a randomly selected node or nodes from the "lower" axilla. The detection of tumor-involved axillary lymph nodes is directly related to the extent of ALND [3]. Thus, the false-negative rate is quite high for both axillary sampling (40%) and level I ALND (10–15%) [4]. Level I–II ALND carries only a 2–3% false-negative rate (due to metastasis above levels I and II). It also has only a 3–9% risk of arm edema, considerably lower than the 10–20% associated with complete ALND. In fact, although complete ALND has the highest rate of tumor detection, its high morbidity has led to recommendations against its routine use.

In 1990 the National Cancer Institute Consensus Conference recommended level I–II ALND for patients with potentially curable breast cancer [5]. Others recommend less or no ALND for certain patients with good prognosis tumors, such as small (T1) malignancies [6,7], who rarely have tumor-involved lymph nodes and should therefore not be subjected to the potential nerve injury and lymphedema associated with more extensive dissection. However, even partial ALND will subject as many as 70–80% of patients with early breast cancer to an operation that detects no metastases.

A promising alternative is sentinel ALND. Sentinel lymphadenectomy was developed to identify regional lymphatic metastases from a primary cutaneous melanoma [8]. The sentinel node, defined as the first node in the regional lymphatic basic that drains a primary tumor, is identified by intraoperative lymphatic mapping using a blue dye injected at the tumor site. The technique of intraoperative lymphatic mapping and sentinel lymphadenectomy has an enviable 1% false-negative rate in melanoma. At the John Wayne Cancer Institute, we have adapted the sentinel node technique to identify axillary metastases in patients with breast cancer. A small amount (3–5 ml) of isosulfan blue dye (Lymphazurin 1%) is injected into the breast tissue immediately surrounding a primary breast carcinoma or a biopsy cavity. An incision is made in the axilla. A blue-staining lymphatic can then be identified and traced proximally and distally to one or more sentinel nodes in the axillary drainage basin.

Our initial trial of intraoperative lymphatic mapping and sentinel ALND in breast carcinoma included 174 consecutive patients; results showed that the technique

Accepted for publication January 15, 1996.
Address reprint requests to Dr. Armando E. Giuliano, John Wayne Cancer Institute, 2200 Santa Monica Blvd, Santa Monica CA 90404.

was both feasible and practical [9]. In this study, all patients underwent sentinel ALND followed by completion ALND, which included level I, level II, and a portion of level III axillary nodes. Sentinel and completion ALND specimens were examined separately, and the incidence of metastases was compared. Although a blue-staining sentinel lymph node was detectable in only 114 of the 174 patients, this node accurately predicted the axillary status of 109 of these patients.

The technique has a definite learning curve. Our rate of sentinel node detection increased from 59% in the first 87 procedures to 72% in the remaining 87 procedures [9]. All false-negative sentinel lymph nodes (sentinel specimen negative when completion specimen positive) belonged to the first 87 cases, and two were in the first five. We found on review that some sentinel nodes identified as tumor-negative by hematoxylin and eosin (H&E) staining became tumor-positive when re-examined by immunohistochemical staining. We therefore introduced routine immunohistochemistry with antibodies to cytokeratin for all sentinel lymph nodes not shown to have metastases on frozen section or with permanent H&E staining. We further developed a rigorous protocol: if the intraoperative frozen section shows no tumor, six to eight faces of the sentinel node are examined for microscopic metastases by H&E and immunohistochemistry.

Our follow-up study of intraoperative mapping and sentinel ALND examined the detection of axillary metastases in 134 patients undergoing complete ALND and in 162 patients undergoing sentinel ALND followed by completion ALND [10]. Both groups were similar in age, percentage palpable primary tumors, size of primary tumor, and total number of axillary lymph nodes examined. Nonsentinel ALND specimens were examined only by H&E; sentinel ALND specimens were also examined with the immunohistochemistry protocol described above. The detection of axillary metastases and micrometastases was significantly higher in patients undergoing sentinel ALND (42% and 38%, respectively) than in those undergoing complete ALND only (29% and 10%, respectively) ($P < 0.03$ and 0.0005). Sentinel ALND with immunohistochemistry thus increases the sensitivity of axillary staging. Although some have questioned the value of detecting micrometastases, others suggest that the detection of micrometastases by immunohistochemistry is prognostically significant [11].

It is worth noting that the addition of immunohistochemistry to the histopathologic workup of a sentinel specimen is not particularly time-consuming, because there are only one or two sentinel nodes. Moreover, most pathologists are already skilled users of immunohistochemical techniques. However, all surgeons require some training and experience with the technical aspects of any new operative technique. In the case of sentinel node mapping, initial frustration is inevitable: it is not easy to recognize a small dye-filled lymphatic embedded in axillary fat. And it can be extremely difficult to dissect the lymphatic proximally and distally in order to identify the first blue-staining node. Sometimes a deep-blue node will stand out against a background of yellow fat, but quite often there is just a subtle blue coloration on the efferent side of the lymph node. Another complicating factor is the timing of dye injection. Dye injected in the lower hemisphere, particularly the lower inner quadrant, takes longer to travel to the axilla than does dye injected in the upper outer quadrant, especially if the breast is large. Positioning the injection needle can also be a problem: it is too easy to inject dye into a biopsy cavity rather than the cavity walls. Plus, inner hemisphere lesions may drain to the internal mammary nodes. Also, some lesions drain only to level III nodes, which are not detected by sentinel node mapping or, for that matter, by routine dissection of levels I and II. We have begun using preoperative lymphoscintigraphy to identify the drainage basins for inner quadrant lesions but as yet have performed sentinel internal mammary lymphadenectomy in only a few cases.

The surgical oncology fellows in our training program usually become confident in their use of intraoperative mapping and sentinel ALND after undertaking about 10–20 cases with supervision. For those surgeons who wish to try sentinel node mapping, we recommend routine completion ALND until sentinel ALND has been mastered as a predictable, reproducible technique. Once mastered, intraoperative lymphatic mapping with sentinel ALND becomes a sophisticated and accurate means of determining lymph node status without the morbidity of total dissection. It can be done on an outpatient basis under local anesthesia with sedation, or with a light general anesthetic. The use of intraoperative radionuclides [12] seems to complicate the procedure enormously and is not likely to increase its accuracy significantly.

Our current experimental protocol for the intraoperative staging of breast cancer consists of sentinel ALND with intraoperative frozen section. If the sentinel lymph node shows metastatic cancer, we complete the axillary dissection. If the sentinel lymph node shows no evidence of metastases, the procedure is terminated without completion ALND. In less than 10% of patients, a sentinel specimen will show metastases only on permanent H&E staining or immunohistochemistry; in this case, we perform completion ALND several days later.

Our results to date are extremely encouraging. In our last 100 consecutive breast cancer patients undergoing sentinel followed by completion ALND, the sentinel specimen was 100% predictive of axillary status, and the rate of sentinel node detection was 93%. Although no procedure is foolproof, intraoperative lymphatic mapping with sentinel ALND enhances the accuracy and decreases the cost and morbidity of staging breast cancer, as com-

pared to routine total or partial ALND. It is important to realize that the sentinel node concept focuses on a tumor's ability to spread to the axilla, rather than its pattern of metastasis. Thus, it does not support the Halstedian view of sequential spread from the primary to the axillary lymph nodes and then to systemic sites. It also does not argue against the more modern notion of axillary involvement as a sign of disseminated disease. Until there are new tumor markers or new imaging techniques to identify axillary metastasis without operative intervention, sentinel ALND represents a highly accurate, minimally invasive alternative.

ACKNOWLEDGMENT

This work was supported by funding from the Joyce and Ben Eisenberg Foundation, Los Angeles, California.

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